Divergent roles of ALS-linked proteins FUS/TLS and TDP-43 intersect in processing long pre-mRNAs.

Journal: Nat Neurosci

Publication Year: 2012

Authors: Clotilde Lagier-Tourenne, Magdalini Polymenidou, Kasey R Hutt, Anthony Q Vu, Michael Baughn, Stephanie C Huelga, Kevin M Clutario, Shuo-Chien Ling, Tiffany Y Liang, Curt Mazur, Edward Wancewicz, Aneeza S Kim, Andy Watt, Sue Freier, Geoffrey G Hicks, John Paul Donohue, Lily Shiue, C Frank Bennett, John Ravits, Don W Cleveland, Gene W Yeo

PubMed link: 23023293

Funding Grants: RNA Binding Protein-mediated Post-transcriptional Networks Regulating HPSC Pluripotency, Neural and general splicing factors control self-renewal, neural survival and differentiation

Public Summary:
Amyotrophic lateral sclerosis is a debilitating adult onset neurodegenerative diseases with no cure. Mutations in two RNA binding proteins TDP-43 and FUS/TLS are causative of ALS. RNA binding proteins interact with hundreds to thousands of RNA targets. Here we identify the RNA targets of FUS/TLS in mouse brains and validate the relevance of these targets in human stem cell-derived neural progenitors and neurons. We find a small set of 45 genes that are misregulated when either FUS/TLS or TDP-43 are depleted. Supporting a common loss of function pathway, we see that a few of these genes are also depleted in sporadic ALS patient motor neurons that have TDP-43 aggregates.

Scientific Abstract:
FUS/TLS (fused in sarcoma/translocated in liposarcoma) and TDP-43 are integrally involved in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia. We found that FUS/TLS binds to RNAs from >5,500 genes in mouse and human brain, primarily through a GUGGU-binding motif. We identified a sawtooth-like binding pattern, consistent with co-transcriptional deposition of FUS/TLS. Depletion of FUS/TLS from the adult nervous system altered the levels or splicing of >950 mRNAs, most of which are distinct from RNAs dependent on TDP-43. Abundance of only 45 RNAs was reduced after depletion of either TDP-43 or FUS/TLS from mouse brain, but among these were mRNAs that were transcribed from genes with exceptionally long introns and that encode proteins that are essential for neuronal integrity. Expression levels of a subset of these were lowered after TDP-43 or FUS/TLS depletion in stem cell-derived human neurons and in TDP-43 aggregate-containing motor neurons in sporadic ALS, supporting a common loss-of-function pathway as one component underlying motor neuron death from misregulation of TDP-43 or FUS/TLS.